disease progression and development of drug resistance, we also know that an individual has the best chance of attaining long-term treatment success by starting treatment as soon as possible after diagnosis when CD4 concentrations are high.[9] Therefore, the identification of individuals as HIV positive as efficiently and as soon as possible is important; WHO has recently introduced a strategy termed 90-90-90 that seeks to identify 90% of people in the world who are HIV positive, to treat 90% of such people, and to attain a non-detectable viral load in 90% of such cases after treatment initiation. The hope is that this will also serve to prevent onward HIV transmission because individuals who have undetectable viraemia are unlikely to be infectious for their partners.[10–12]

Of course, the success of the WHO 90-90-90 guidelines depends on convincing a very high proportion of high-risk individuals who are unaware of their HIV status to agree to be tested. In this context, a sound argument can be made that more effective incentivisation is urgently needed and perhaps a financial offering could make a difference. Although the costs of such a programme could be high, these would almost certainly be dwarfed by the costs involved in providing antiretroviral treatment to people who might become infected by those who have not yet undergone therapy because their HIV status is unknown.

Altogether, the results of this study are a reminder that the problems of HIV drug resistance and transmitted drug resistance are very real, especially in developing country settings, and that there is a need for enhanced, cost-effective tests that can screen for drug resistance in parts of the world in which such tests are often not affordable as well as for more effective screening for HIV infection in the first place.

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# Mounting evidence for use of artemisinin derivatives for malaria in early pregnancy

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Malaria in pregnancy can be a clinically devastating condition, and exacts substantial morbidity and mortality in vulnerable populations particularly in the developing world.[1] Its complications are conspicuous in pregnant women who are prone to severe anaemia, and their offspring face possibilities of still births, miscarriages, or low birthweight.[2]

To prevent malaria in pregnancy and its complications, various measures to reduce human–malaria vector contact such as the use of insecticide-treated nets and insecticide residual spraying are applied extensively. Chemoprevention with sulfadoxine–pyrimethamine is used to mitigate adverse pregnancy outcomes, but is also largely


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compromised by resistance.[3] Furthermore, these measures are not foolproof in that acquisition of malaria still occurs. Therefore, chemotherapy is imperative to eliminate the infection and prevent complications.

Many endemic countries now recommend artemisinin-based combinations as first-line treatment of malaria in the general population.[4] Therefore, their widespread use makes inadvertent exposure in early pregnancy inevitable.[5]

Although substantial information has accumulated to support the safe use of certain artemisinin derivatives as the most appropriate drugs for treatment of malaria in the second and third trimesters of pregnancy, more evidence is needed to support their safe use in the first trimester. Concerns about embrotoxicity and possible teratogenicity have led to extreme caution about the use of artemisinin derivatives in early pregnancy.[6] The general recommendation is to use artemisinins only when the benefits outweigh the consequences of the infection. To that effect, clinical trials of artemisinin derivatives in early pregnancy have been slow in coming, because extreme caution is required to avoid untoward outcomes or missing out subtle damages that might be caused by the drugs.[7]

Systematic information about the safety of artemisinin derivatives in the early pregnancy comes from observational studies including pregnancy registries, particularly in situations where the drugs are taken inadvertently.[5] Such studies have many limitations including absence of rigor to estimate the period and duration of exposure and inability to account for confounding factors or to detect subtle and long-term adverse outcomes in the offspring.[7]

In *The Lancet Infectious Disease*, Kerryn A Moore and colleagues[8] report a large study describing a prospective observation of 2558 women with first-trimester malaria and analyses of 183 with initial exposure to various artemisinin derivatives. The study gives more precise details than previous studies about exposure to quinine and the available artemisinin derivatives, their doses, and the duration of exposure. The study affirms the association between infection with either vivax or falciparum malaria and miscarriages, and underscores the importance of treatment with efficacious drugs such as artemisinins in the first trimester to avoid adverse outcomes.[9] The investigators uniquely estimate the gestation period of exposure (including the embryo-sensitive period) to the artemisinin derivatives, and by use of so-called left truncation they have accounted for confounding from other causes of miscarriages.[10] This study, in our view, presents a unique and innovative approach to the generation of rigorous evidence for safety of artemisinin derivatives when used in early pregnancy.

Although recent studies have shown encouraging results from some artemisinin derivatives, more data are still needed to ascertain the safety of many other artemisinin derivatives in pregnancy. For example, there is mounting evidence about the use of artemether–lumefantrine, but more safety information is needed on such drugs as dihydroartemisinin–piperaquine, which is highly efficacious, has a simple treatment regimen, and has a relatively long protective period following intake—an attribute that should be of important, especially in areas of high transmission.[11]

Similar to other drugs under observation, artemisinin-based combinations need to be subjected to intense pharmacovigilance to ensure that subtle anomalies or genetically related effects, some of which might manifest in the long term, are identified and documented.[7] Genetic differences in the metabolism of various components of the derivatives are still a concern, so studies in diverse populations are needed to generate information across different ethnic groups.

With this strong evidence from this study, large randomised trials are justified to be undertaken at this stage to investigate other effects that might not have been shown in study designs reported previously. The study further shows that artemisinins are as safe as quinine, and can be used safely in the first trimester. It has made a strong case to support the acceleration of the processes for recommending the use of artemisinin derivatives for treating malaria during the whole period of pregnancy.

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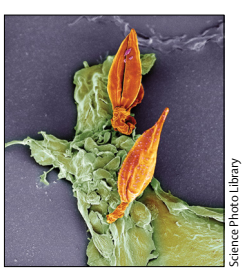
# Estimations of cutaneous leishmaniasis burden: a constant challenge

Leishmaniases has the ninth largest diseases burden among the 13 parasitic and bacterial neglected tropical diseases.[1–3] Knowledge of these diseases is poor, information on their global occurrence is disparate and sparse, and their actual burden remains uncertain.[4] Establishing the burden of cutaneous leishmaniasis is challenging because of the difficulty of extrapolation from official data sources.

In *The Lancet Infectious Diseases*, Chante Karimkhani and colleagues[5] report the burden of cutaneous leishmaniasis in 152 countries and assess the distribution of cutaneous leishmaniasis burden across different regions. Andean Latin America, North Africa and Middle East, western sub-Saharan Africa, and south Asia had the most disability-adjusted life-years lost to leishmaniasis. Also, among the 20 countries with the highest incidence rates worldwide, 14 are in these regions. The burden of leishmaniasis in these regions is most likely a consequence of both biotic (including the presence of sandflies and mammals) and abiotic factors (eg, land surface temperature, normalised difference vegetation index, and precipitation) enabling stable transmission in these regions.[6] Environmental and socioeconomic factors might also affect the distribution of cutaneous leishmaniasis. An estimated 1·71 billion people live in areas where environmental factors potentially predispose people to cutaneous leishmaniasis.[7] Furthermore, burden of leishmaniasis disproportionately affects the poorest people. Poor housing conditions, environmental sanitation, and lack of personal protective measures lead to an increase of risk of infection in such populations.[8] Karimkhani and colleagues'[5] analysis of country-level data shows the unequal distribution of disease burden—mostly related to urbanisation. Other factors could also explain this inequality, including the presence of control measures focused on cutaneous leishmaniasis, population awareness, and climate change. A strong association has been reported between climate factors (temperature, relative humidity, rainfall, and evaporation) and monthly incidence of zoonotic cutaneous leishmaniasis in Golestan Province, Iran.[9]

Since the 1993 World Development Report, policy makers have used disability-adjusted life-years lost to estimate disease burden—now the most widely used measure of disease burden.[10,11] Nevertheless, the accuracy disability-adjusted life-years depends on the reliability of incidence estimates. Indeed, the main hindrance of epidemiological investigation is underestimation of incidence, linked to under-reporting. In Guatemala and Jordan, the incidence of cutaneous leishmaniasis has been reported to be underestimated by 40–47-fold in national surveillance data.[12,13] Such limitations led Karimkhani and colleagues to use a correction factor for under-reporting to estimate prevalence and incidence. Because of the uncertainties inherent in available



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